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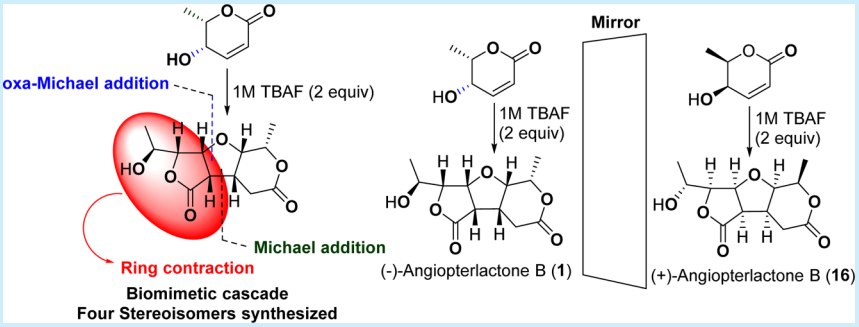
Biomimetic Total Synthesis of Angiopterlactone B and Other Potential Natural Products

Tharun K. Kotammagari,[†,‡] Rajesh G. Gonnade,[§] and Asish K. Bhattacharya*[,†,‡]

[†]Division of Organic Chemistry, [‡]Academy of Scientific and Innovative Research, and [§]Centre for Material Characterization, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411 008, India

Supporting Information



ABSTRACT: A one-pot biomimetic synthesis of (−)-angiopterlactone B and its enantiomer (+)-angiopterlactone B has been accomplished via TBAF-catalyzed tandem ring contraction followed by oxa-Michael/Michael addition sequence. Comparison of specific optical rotations, absolute configurations, and CD spectra of natural, synthesized (−)-angiopterlactone B and (+)-angiopterlactone B unequivocally proves that the isolated angiopterlactone B must be levorotatory. Synthesis of hitherto undiscovered natural products **18** and **20** and analogues of angiopterlactone B demonstrate the versatility of this method.

(+)-Angiopterlactone B (**1**) and angiopterlactone A (**2**) were isolated from the Asian fern *Angiopteris caudatiformis* (Angiopterdaceae) by Zou et al.[1] (Figure 1). Angiopterlactone B (**1**) has a unique structure; i.e., it is a tricyclic ring system (A/B/C) having dual lactones flanking both sides of a tetrahydrofuran ring containing seven contiguous stereocenters. Lactones **3** and **4** were reported[1] to be naturally co-occurring along with compounds **1** and **2**, and it has been stated[2] that angiopterlactone A (**2**) is biosynthesized in the plant from compounds **3** and **4**. Further, Zou et al.[1] reported that angiopterlactone A (**2**) could be a biosynthetic precursor of angiopterlactone B (**1**). However, in the isolation paper,[1] the authors did not establish the stereochemistries of lactones **3** and **4**.

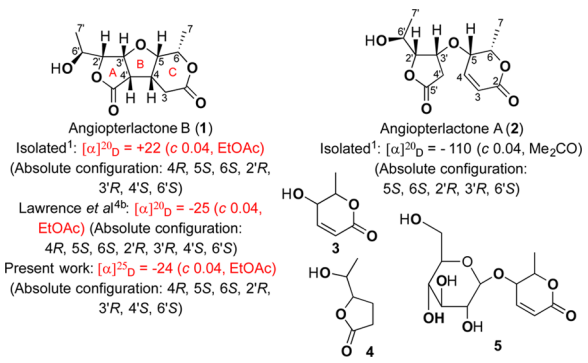


Figure 1. Structure of angiopterlactone B (**1**) and co-occurring lactones **2**−**5** from *A. caudatiformis*.

The unique structural features of angiopterlactone B (**1**) were hitherto unknown in the literature,[3] thus making this compound an interesting target for total synthesis.[4a] In the isolation paper, Zou et al.[1] reported a negative Cotton effect for angiopterlactone B (**1**) [absolute configuration: 4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*]. However, they mentioned that its optical rotation was $[\alpha]_D^{20}$ +22 (*c* 0.04, EtOAc). We wished to mimic the biosynthesis of angiopterlactone B (**1**) and also to clear the ambiguity with its specific rotation. While our manuscript was being prepared, we came across a publication from Lawrence et al.[4b] on the synthesis of (−)-angiopterlactone B. Our retrosynthesis is depicted in Scheme 1. We envisaged that angiopterlactone B (**1**) could be obtained by intramolecular Michael addition of angiopterlactone A (**2**). Angiopterlactone A (**2**) could potentially be synthesized by the intermolecular oxa-Michael[5,6] addition reaction of the five-membered lactone **7** and the six-membered lactone **8**. The six-membered lactone **8**, in turn, could be obtained from di-*O*-acetyl-L-rhamnal **6** by the application of Ferrier rearrangement[7] followed by C-4 epimerization using the Mitsunobu reaction. The five-membered lactone **7** could be obtained from **6** by oxidative rearrangement followed by hydrolysis and translactonization.

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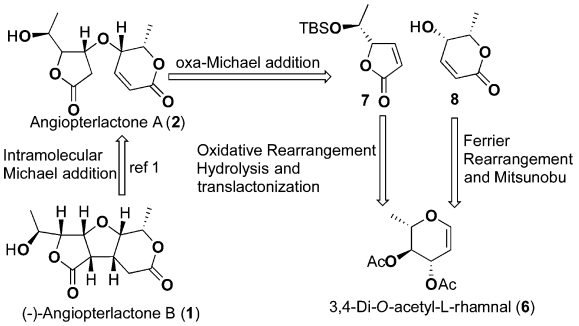
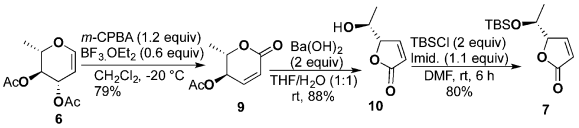
Scheme 1. Retrosynthetic Plan for Synthesis of Angiopterlactone A (2) and Angiopterlactone B (1)



The α,β-unsaturated γ-lactone **7** fragment for Michael addition was prepared from the 3,4-di-*O*-acetyl-L-rhamnal **6** in three steps (Scheme 2). Oxidative rearrangement of 3,4-di-*O*-acetyl-L-

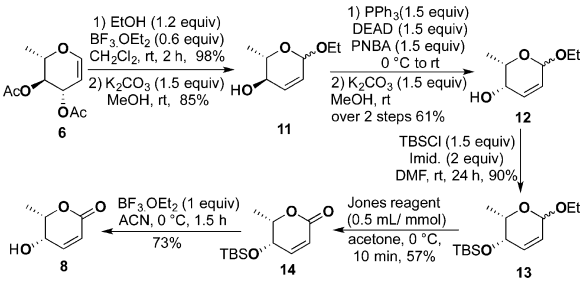
Scheme 2. Synthesis of Five-Membered α,β-Unsaturated γ-Lactone 7



rahmnal **6** according to the method reported by Lichtenthaler et al.[8] furnished ene lactone **9** which on hydrolysis of the acetate group and translactonization with barium hydroxide yielded the desired α,β-unsaturated γ-lactone **10**. The free secondary hydroxyl group was protected as a TBS ether with *tert*-butyldimethyl silyl chloride and imidazole in DMF at room temperature to yield the five-membered α,β-unsaturated γ-lactone **7**.

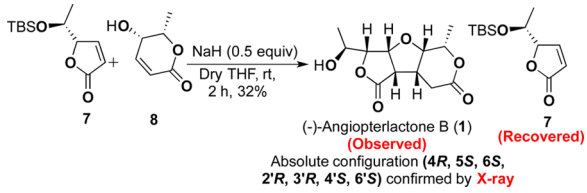
The key six membered lactone, fragment **8**, was also synthesized starting from 3,4-di-*O*-acetyl-L-rhamnal **6** by following a reported procedure[9] (Scheme 3).

Scheme 3. Synthesis of Six-Membered α,β-Unsaturated δ-Lactone (8)



With both fragments in hand (**7** and **8**), we attempted to synthesize angiopterlactone A (**2**) using intermolecular oxa-Michael addition reaction. When a mixture of compounds **7** and **8** (1.0 equiv each) was treated with NaH (0.5 equiv) in dry THF (Scheme 4), we obtained a single product. However, the product did not show any peaks for the corresponding olefins in the ^{1}H NMR spectrum as required for the oxa-Michael addition product. Instead, (−)-angiopterlactone B (**1**) was formed as evidenced by the ^{1}H NMR spectrum,[1,4,10] which was further corroborated by ^{13}C/HSQC and HMBC NMR experiments and HRMS (see the Supporting Information, SI, for full details). Finally, we proved

Scheme 4. Formation of Angiopterlactone B (1) via Tandem Ring Contraction/Oxa-Michael/Michael Addition Sequence



unequivocally the structure of (−)-angiopterlactone B (**1**) by its single-crystal X-ray analysis[11] (Figure 2a).

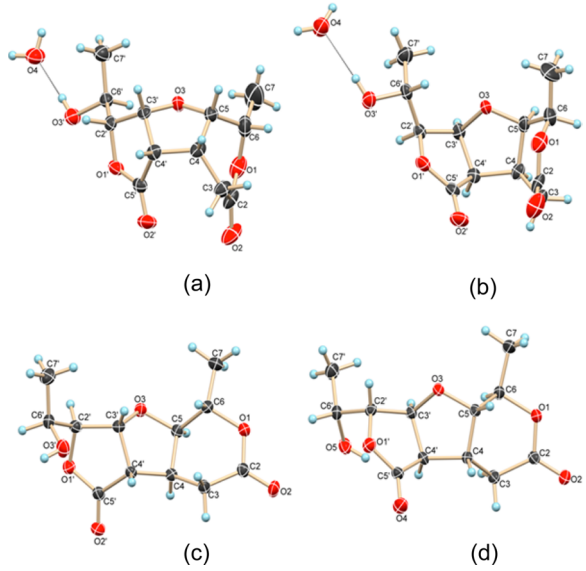


Figure 2. ORTEP diagrams of (a) (−)-angiopterlactone B (**1**), (b) (+)-angiopterlactone B (**16**), (c) compound **18**, and (d) compound **20**.

It is interesting to mention here that compound **7** was recovered unreacted from this reaction. This suggested that only the six-membered lactone **8** provides both the five-membered and six-membered partners to furnish compound **1**. A screen of various bases ultimately revealed that TBAF[12] was the best, with compound **1** being formed in 62% yield (see the SI for full details). Since six-membered lactones are sensitive to bases,[13] TBAF was selected as a mild base and found to efficiently catalyze this tandem ring contraction/oxa-Michael/Michael addition sequence.

Based on the results obtained in Scheme 4 (i.e., recovery of unreacted compound **7**), we propose a biomimetic pathway[4b,14−16] for the formation of the tricyclic ring system (A/B/C) of (−)-angiopterlactone B (**1**) by TBAF that follows a domino reaction sequence, which has been delineated in Scheme 5. First, the fluoride ion of TBAF abstracts a proton from the six-membered lactone **8** leading to ring contraction to form the stable five-membered α,β-unsaturated γ-lactone **10**. Oxa-Michael addition reaction between lactone **10** and the six-membered lactone **8** then takes place to furnish intermediate **A**. The intermediate **A**, on intramolecular Michael addition, furnishes intermediate **B** which, on protonation, leads to the formation of (−)-angiopterlactone B (**1**).

It is pertinent to mention here that our synthesized angiopterlactone B (**1**) showed a negative Cotton effect in the circular dichroism (CD) (see the SI for full details) spectrum with as optical rotation $[\alpha]_D^{25}$ −24 (*c* 0.04, EtOAc). However, Zou et

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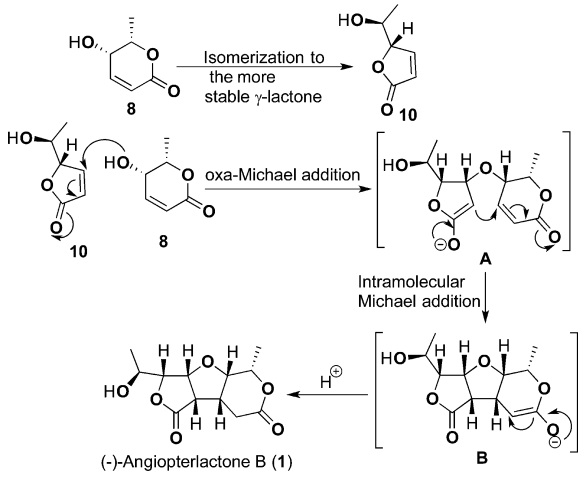
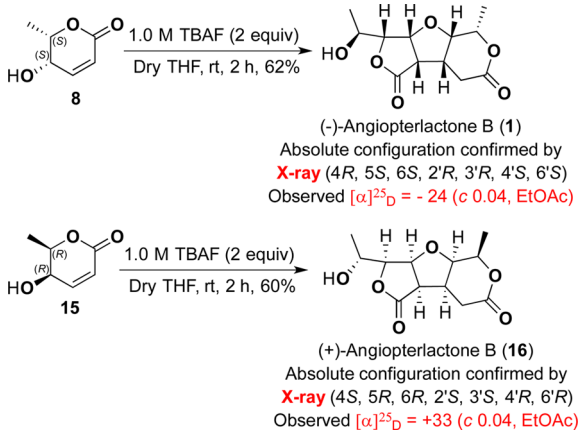
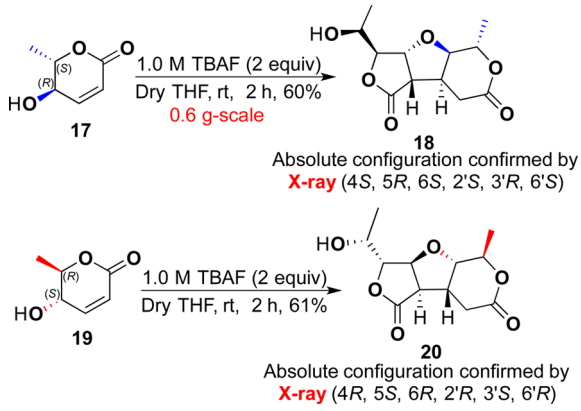
Scheme 5. Proposed Biomimetic Pathway for the Formation of (−)-Angiopterlactone B (1)



Scheme 6. Synthesis of (−)-Angiopterlactone B (1) and (+)-Angiopterlactone B (16) with TBAF



Scheme 7. Synthesis of Hitherto Unreported Natural Products (Diastereomers of Angiopterlactone B)



al.[1] reported a negative Cotton effect in the CD spectrum with optical rotation $[\alpha]_D^{25}$ +22 (*c* 0.04, EtOAc) for the isolated natural **1**. Angiopterlactone B (**1**) synthesized by us and Lawrence et al.[4b] showed negative optical rotation. Since the absolute configurations of natural angiopterlactone B isolated by Zou et al.[1] and synthesized by Lawrence et al.[4b] and us were found to be similar by single-crystal X-ray analysis, we opined that the ambiguity revolved around its optical rotation only. We also considered the possibility that Zou et al.[1] might have obtained a levorotatory sign for angiopterlactone B (**1**) but mistakenly reported the wrong sign in their publication.

Since the discrepancy in the signs of synthesized angiopterlactone B (**1**) (levorotatory) was observed with the isolated[1] angiopterlactone B (**1**) (dextrorotatory) (Table 1), we decided to synthesize the other enantiomer of (−)-angiopterlactone B (**1**) in order to clear the ambiguity. For this, we utilized 4-*epi*-(+)-osmundalactone **15**,[17] which is an enantiomer of lactone **8**, for the base-catalyzed (TBAF) tandem ring contraction/oxa-Michael/Michael addition sequence to afford (+)-angiopterlactone B (**16**) (Scheme 6). The complete structure was elucidated by NMR spectroscopy and by single-crystal X-ray analysis[11] (Figure 2b). Indeed, our supposition was proven correct with (+)-angiopterlactone B (**16**) showing a positive Cotton effect with optical rotation $[\alpha]_D^{25}$ +33 (*c* 0.04, EtOAc) (see the SI for full details). Our synthesis of (+)-angiopterlactone B (**16**) has now cleared the ambiguity in the signs of the optical rotation and proves unequivocally that the natural angiopterlactone B (**1**) must be levorotatory (Table 1). The other possible diastereomers of (−)-angiopterlactone B (**1**) were synthesized by base-catalyzed (TBAF) tandem ring contraction/oxa-Michael/Michael addition reactions on 5,6-dihydropyran-2-one (**17**)[9] and (+)-osmundalactone (**19**)[17,18] to furnish compounds **18** and **20**, respectively (Scheme 7). This biomimetic base-catalyzed tandem reaction can be performed on gram-scale also, as the synthesis of compound **18** has been accomplished on gram scale. Compounds **18** and **20** are enantiomers of each other, and their complete structure was elucidated using NMR spectroscopy and by their single-crystal X-ray analyses[11] (Figure 2c,d). The enantiomers, compounds **18** and **20**, showed a negative Cotton effect with optical rotation $[\alpha]_D^{25}$ −106 (*c* 0.1, acetone) and a positive Cotton effect with optical rotation $[\alpha]_D^{25}$ +105 (*c* 0.7, acetone), respectively, in the circular dichroism (CD) spectra (see the SI for full details). Interestingly, diastereomers **18** and **20** are yet to be isolated from natural sources. However, our synthesis adds to the growing number of instances of natural product anticipation through biomimetic synthesis.

Various substituted 5,6-dihydropyran-2-ones were synthesized from tri-*O*-acetyl-D-glucal (see the SI for full details) in order to generalize the base-catalyzed tandem ring contraction/oxa-Michael/Michael addition reactions that furnish tricyclic ring

Table 1. Absolute Configurations, Specific Rotations, and CD Spectra of Natural and Synthetic Angiopterlactone B

	absolute configuration	specific rotation	circular dichroism
Zou et al.[1] (isolation)	4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*	$[\alpha]_D^{20}$ = +22 (*c* 0.04, EtOAc)	negative Cotton effect
Lawrence et al.[4b] (through biomimetic synthesis)			
(−)-angiopterlactone B	4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*	$[\alpha]_D^{20}$ = −25 (*c* 0.04, EtOAc)	
this work (through biomimetic synthesis)			
(−)-angiopterlactone B	4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*	$[\alpha]_D^{25}$ = −24 (*c* 0.04, EtOAc)	negative Cotton effect
(+)-angiopterlactone B	4*S*,5*R*,6*R*,2′*S*,3′*S*,4′*R*,6′*R*	$[\alpha]_D^{25}$ = +33 (*c* 0.04, EtOAc)	positive Cotton effect

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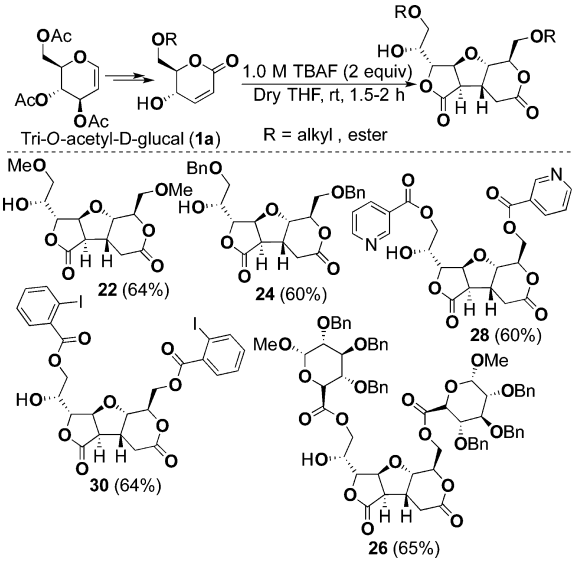
system (A/B/C) having dual lactones. These substituted 5,6-dihydropyranones, on reaction with TBAF in dry THF, afforded the corresponding analogues of angiopterlactone B (**1**) (Scheme 8). The synthesis of diverse analogues demonstrates the

Scheme 8. Synthesis of Analogues with Substituted Dihydropyrones



robustness of our TBAF methodology. It is pertinent to mention here that fusion of rings A and C to the tetrahydrofuran ring (B) takes place in a *cis*-manner to furnish the tricyclic ring system (A/B/C) irrespective of the streochemistries at C-4 and C-5 of the 5,6-dihydropyran-2-ones.

In summary, we have accomplished a biomimetic total synthesis of naturally occurring angiopterlactone B (**1**) from 5,6-dihydropyran-2-one, utilizing a TBAF (base)-catalyzed tandem ring contraction/oxa-Michael/Michael addition sequence in one pot. Also, we have been able to prove unequivocally that natural angiopterlactone B (**1**) must be levorotatory by carrying out a synthesis of (+)-angiopterlactone B (**16**). Diastereomers (**18** and **20**) of angiopterlactone B (**1**), which are hitherto undiscovered natural products, were also synthesized using our developed methodology. Further, we have explored this methodology on various substituted 5,6-dihydropyranones to afford analogues of angiopterlactone B (**1**). Our developed method utilizes simple 5,6-dihydropyran-2-ones as starting materials to synthesize complex tricyclic ring system in one step. The fusion of two lactones (A and C) to form the core tricyclic ring was found to be *cis* in all of the synthesized compounds irrespective of the streochemistries of the starting 5,6-dihydropyran-2-ones. We believe that our synthetic strategy will provide various complex tricyclic ring systems for further biological studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01525.

Experimental procedures and analytical data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ak.bhattacharya@ncl.res.in.

ORCID

Rajesh G. Gonnade: 0000-0002-2841-0197

Asish K. Bhattacharya: 0000-0002-9162-522X

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Krishna N. Ganesh, IISER-Pune, on the occasion of his 65th birthday.

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(10) Zou et al.[1] had recorded NMR of natural angiopterlactone B in $CDCl_3$. However, we observed that our synthesized angiopterlactone B was sparingly soluble in $CDCl_3$ at ambient temperature. We found that it was freely soluble in acetone-d_6, and hence, we recorded our NMR in acetone-d_6. We wrote e-mails to Prof. Zou to clarify issues related to the solubility of isolated angiopterlactone B and the discrepancy in its optical rotation. However, our e-mails remain unanswered. Lawrence et al.[4b] have also recorded NMR spectra of their synthesized (−)-angiopterlactone B in CD_3OD. Hence, we have recorded our NMR spectra in CD_3OD for comparison (see comparison table provided in the Supporting Information).

(11) Crystallographic data (excluding structure factors): CCDC-1525957−1525961 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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